REMARKS

This is in response to the Office Action mailed on June 30, 2004, and the references cited therewith.

Claims 10 and 24 are amended, no claims are canceled, and no claims are added; as a result, claims 1-28 are now pending in this application.

Claims 10 and 24 are amended to correct a typographical error that was introduced during prosecution of the parent case (U.S. Patent Application Serial No. 09/869,141, now U.S. Patent No. 6,667,302). In claim 10 of the parent case, a carbonyl was deleted from the group -N(H)-C(=O)-C(=O)-N(H)-, to incorrectly recite -N(H)-C(=O)-N(H)-. The error was inadvertently duplicated in claims 10 and 24 of the instant application. Claims 10 and 24 are amended herein to correct the errors. Support for the amendments is found in each of the priority documents, namely U.S. Patent Application Serial No. 09/869,141 (now Patent No. 6,667,302); PCT/US98/27822, and U.S. Provisional Application 60/070,287 (see specifically claim 10 of each of the priority applications as filed). Additional support is found in the instant application as filed, where -N(H)-C(=O)-C(=O)-N(H)- is specifically recited at page 6, lines 24 and 33, and at page 7, lines 2 and 4.

No new matter has been added by way of the amendments. The amendments are supported by the specification and do not limit the scope of the claims in any way. Accordingly, once allowed, these claims will be entitled to a full scope of equivalents.

§112 Rejection of the Claims

Claims 1-28 were rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly fails to provide information that would allow the skilled artisan to fully practice the instant invention without undue experimentation. This rejection is respectfully traversed.

The test for enablement is whether one reasonably skilled in the art could make or use the invention from the disclosure in the specification coupled with information known in the art without undue experimentation. M.P.E.P. § 2164.01(a) (citing *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 U.S.P.Q.2d 1217, 1223 (Fed. Cir. 1988)). The Federal Circuit put forth relevant factors to consider when determining whether experimentation is undue. These factors

include: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples relating to the invention; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. A determination that undue experimentation would have been needed to practice the claimed invention is not a single, simple factual determination. Rather, it is a conclusion that can only be reached by weighing all factual considerations, including the eight factors identified above. In re Wands, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988).

Applicant respectfully points out that the Examiner has set forth an incorrect legal standard for enablement with respect to Applicant's claims. On page 2 of the Office Action, last three lines, the Examiner states "The specification does not provide sufficient information that all cancers are treatable by all bis-benzimidazoles described in the methods claimed." (emphasis in the original.) The correct standard was identified in In re Wands. An analysis of claims 1-28 against this standard is provided below. Applicant's claims recite methods for inhibiting cancer cells using an effective amount of a compound of formula I (see e.g., independent claims 1 and 15). The instant specification specifically teaches that compounds of formula I are potent topoisomerase I poisons (page 14, line 1), and that topoisomerase inhibitors are known to be useful to inhibit cancer cells (page 1, lines 16-19; page 14, lines 2-7). The specification identifies a test for determining the cancer cell inhibiting properties of a given compound (Test B, page13), and provides working examples that show that representative compounds inhibit cancer cell growth in human cell lines (Table 1, page 13). Additionally, the claims recite an effective amount, thus excluding inoperable embodiments. As such, the enablement of the specification is commensurate with the scope of the claims. Because the specification enables the claimed subject matter as it is recited, a rejection under 35 U.S.C. § 112, first paragraph, is improper.

Claims 1-28:

Independent claims 1 and 15 recite methods of inhibiting cancer cells. An analysis of the Wands factors shows that it would not require undue experimentation to practice the present invention as claimed.

(1) *The quantity of experimentation necessary.* When analyzing whether "undue experimentation" is required to practice claimed methods, the key word is "undue" not "experimentation." In re Angstadt, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976). Enablement is not precluded by the necessity for some experimentation, such as performing routine assays. In fact, a considerable amount of experimentation is permissible if the experimentation is merely routine, or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should take. Ex parte Jackson, 217 U.S.P.Q. 804, 807 (Bd. App. 1982).

Claims 1 and 15 recite methods of inhibiting cancer cells. A pharmacological model for determining the ability of a compound to inhibit cancer cell growth is provided at page 13 of the specification (Test B). Test B is a standard screen that can be routinely employed by workers in this field. It would be improper to maintain that undue experimentation is required for a skilled artisan to determine if a compound of the invention inhibits cancer cells because the specification actually provides an appropriate screen. Such screens are routinely employed in this field. Screening a claimed compound does not constitute "undue experimentation," particularly in an art where the skill level is high. In re Wands, 8 U.S.P.Q.2d at 1404.

(2) *The amount of direction or guidance presented.* Applicant's specification provides sufficient guidance to allow one of skill in the art to practice the claimed invention. Additionally, the specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation. M.P.E.P. § 2164.02. The specification contains 9 pages of guidance for preparing representative compounds and compositions (pages 8-12 and page 15-18), and 2 pages describing appropriate screening procedures (Tests A and B, pages 12-13). Applicant has therefore provided ample disclosure, with respect to methods of inhibiting cancer cell growth with an effective amount of a compound of formula I, to enable the skilled artisan to practice the invention as claimed. One skilled in the art, if necessary, can also properly look to the state of the art of cancer cell inhibition for useful guidance with respect to screening and determining the inhibitory activities of the claimed compounds. Applicant thus respectfully submits that the disclosure, coupled with knowledge in the art at the time the application was filed, provides an

adequate amount of direction and guidance to adequately enable one of skill in the art to inhibit cancer cells using the claimed compounds.

(3) *The presence or absence of working examples relating to the invention.* The specification contains working examples of the invention. At page 13 of the specification, a screen for determining cytotoxicity against cancer cells (Test B) is described. Actual data from Test B is provided for two claimed compounds. Representative compounds (**2** and **3**) inhibited cancer cells in two different human cancer cell lines (Table 1). By reviewing the working example provided in the specification, one skilled in the art would understand how to test a given compound for cancer cell inhibiting properties, and would understand that representative compounds of formula I do in fact inhibit cancer cells. The instant specification therefore contains working examples that clearly demonstrate that cancer cell growth can be inhibited using the claimed methods.

(4) *The nature of the invention* and (5) *The state of the prior art.* The nature of the invention is a method of inhibiting cancer cell growth. Medicinal chemistry and pharmacology are mature fields. Cancer has been known for decades, has been well researched, and a variety of agents and methods are available to inhibit cancer cell growth. For example, camptothecin and its structurally-related analogs have been extensively studied (page 1, lines 25-27), are known in the art to be topoisomerase I poisons (see page 1, line 25 through page 2, line 3), and topoisomerase I poisons are known to inhibit cancer cell growth. The instant invention thus falls within a well established field. Applicant therefore respectfully submits that the state of the prior art is well developed. As a result, one skilled in the art has access to a significant body of assays and techniques useful to evaluate the cancer cell inhibiting properties of the recited compounds.

(6) *The relative skill of those in the art.* In the pharmaceutical arts, the skilled worker typically has a Ph.D. and often has postdoctoral training. Thus, the relative skill level of those practicing in the art is very high, and screening programs, such as the assays described by Tests A and B (pages 12-13 of the specification) are considered routine.

(7) *The predictability or unpredictability of the art.* The fact that the outcome of a screening program is unpredictable is precisely why a screening program is carried out. The Federal Circuit has explicitly recognized that the need, and methodologies required, to carry out extensive synthesis and screening programs to locate bioactive molecules do not constitute undue

experimentation. In re Wands, 8 U.S.P.Q.2d at 1406-1407. Practitioners of the art are well-equipped to prepare and screen compounds of formula I to identify those compounds that inhibit cancer cell growth. See also, Hybritech Inc. v. Monoclonal Antibodies Inc., 231 U.S.P.Q. 81, 84 (Fed. Cir. 1986) (evidence that screening methods used to identify characteristics [of monoclonal antibodies] were available to the art was convincing of enablement). Thus, the fact that a given compound of formula I would have to be investigated to determine if it is effective to inhibit cancer cell growth does not constitute "undue experimentation" (Ex parte Forman, 230 U.S.P.Q. 546 (Bd. App. 1986)). This is particularly true in an art area where the skill level is very high and in which screening large numbers of compounds has been a standard practice for years.

It is respectfully submitted that one skilled in the art would not necessarily believe that this is an extremely unpredictable art. The specification provides an example of how the claimed methods can be practiced *in vitro* (Test B, page 13). *In vitro* testing against cancerous cell lines in tissue culture is accepted as a standard test to predict *in vivo* anti-cancer efficacy. The skilled artisan would accept that activity against the cell lines reported in Table 1 (page 13) is reasonably predictive of efficacy *in vivo* against the corresponding cancers. This is sufficient to meet the requirements of 35 U.S.C. § 112, first paragraph. M.P.E.P. § 2107.02 (I) and (III).

Additionally, the specification provides Test A (pages 12-13), which allows a practitioner to determine if a compound is a topoisomerase I inhibitor. Thus, one skilled in the art would understand that the mechanism by which the compounds inhibit cancer cell growth is through a topoisomerase I inhibition pathway. The specification further provides information regarding dosages and administration of compounds of the invention that would enable one skilled in the art to practice the claimed method *in vivo* without undue experimentation (page 8, line 19 to page 12, line 13; Example 4; and U.S. Patent No. 4,938,949, which is incorporated by reference).

Furthermore, the compounds of formula I all possess structurally similar cores of bis-benzimidazoles. Because of the defined core structures, the data that is presented in the specification, and the inhibitory activity that is shown, Applicant submits that it would be reasonable for one skilled in the art to believe that the compounds recited in the claims would possess the recited activity. Finally, the claims recite an amount "effective to inhibit said cancer cells" or "an effective amount", which is an amount necessary to carry out the claimed effect.

Thus, whether or not there is some unpredictability, the claims exclude any inoperable embodiments.

(8) *The breadth of the claims*. Claim breadth alone does not provide the basis for a nonenablement rejection. In re Moore, 169 U.S.P.Q. 236 (C.C.P.A. 1971). In the instant case, the claims recite a finite list of compounds, each of which possesses a defined bis-benzimidazole core. The bis-benzimidazole core can be substituted at five specific cites. The substituents R_1-R_5 are selected from a reasonable list of groups commonly found in pharmaceutical agents, many of which have substantial structural similarity. The definitions of R_1-R_5 are not unreasonably broad. Accordingly, Applicant respectfully submits that the claims are not overly broad.

Applicant's comments on the §112, first paragraph rejection:

The Examiner has the burden to establish a *prima facie* case that an applicant's claims are not enabled. The Examiner bears the burden of providing some evidence that the claims are not operative. Applicant's specification, however, provides actual working examples (Test B and Table 1, page 13) specifically showing that representative compounds of the invention do in fact inhibit cancer cells, as recited in the claims. Applicant's specification therefore demonstrates that the claims are operative. Additionally, sufficient guidance is provided for one skilled in the art to practice the claimed invention, as discussed in the Wands analysis above. Applicant respectfully submits that the Examiner's assertion that the claims are not enabled is unsupported by the facts of the instant case. Accordingly, the Examiner has failed to meet the burden required to establish a rejection of claims 1-28 under §112, first paragraph.

Applicant notes that the Examiner stated on page 3 of the Office Action, lines 2-4 under Breadth of the Claims, that "The claims encompass inhibition of any number of cancers by a bisimidazole to be administered in any concentration" (emphasis added). Applicant respectfully points out that the claims do not recite "in any concentration". The claims recite an amount "effective to inhibit said cancer cells" (claim 1) or "an effective amount" (claim 15), each of which is an amount necessary to produce the recited effect. This claim element limits the claims to effective amounts of a compound of formula I and thus does not encompass any concentration. In the same paragraph, the Examiner stated "There are countless possible compounds for the treatment claimed due to the breadth of the substituents: R_1, R_2, R_3, R_4, and R_5." Applicant

disagrees with the Examiner's statement. Each variable (R_1-R_5) has a finite and well defined set of possible values. Accordingly, Applicant has not claimed "countless possible compounds". Additionally, all compounds of formula I have a common bis-benzimidazole core structure.

On page 4 of the Office Action, under Guidance of the Specification, the Examiner stated that "the cytotoxicity of the different compounds were observed to vary by 30 fold, providing little guidance for the expectation of other compounds within the scope of Applicant's claimed invention." This variance in activity is irrelevant to the enablement of the claims by the specification. Applicant has taught that the claimed compounds are topoisomerase I poisons (page 14, lines 1-7) and the specification provides the necessary test for determining the cancer inhibiting effects of the claimed compounds (Test B, page 13). Variance in activity of the claimed compounds does not show that the specification lacks sufficient guidance to practice the invention as claimed. Additionally, the Examiner stated at lines 13-14 of page 4 that compound **4** does not even exhibit any activity as a topoisomerase I poison. Applicant respectfully points out that compound **4** is not included in the definition recited in the claims.

On page 5 of the Office Action, under State of the Art, the Examiner cited Carter, et al. in support of his contention that none of forty known anticancer agents (in 1981) were effective against all cancers. It is respectfully submitted that the Examiner has not used the correct legal standard for determining enablement. The proper standard under 35 U.S.C. § 112, first paragraph, is whether practicing the invention would require undue experimentation (In re Wands), not whether the recited compounds will treat all known types of cancer. The lack of a "silver bullet" as stated in the last line of page 5 is irrelevant to the issue of enablement regarding the claimed invention. Again, it suggests that the Examiner has applied an incorrect legal standard for enablement.

Additionally, the document cited by the Examiner provides insufficient information to determine its relation to Applicant's specification. The document provides no chemical names or chemical structures for the numerous drug abbreviations, and no data is provided to explain the nature of the heading "Drug-Tumor Interaction". Without more information, Carter, et al. appears irrelevant to the instant application, and to the rejection of Applicant's claims.

Furthermore, on page 7 of the Office Action, under The Quantity of Experimentation Necessary, the Examiner discusses several procedures routinely performed by workers in the

pharmaceutical arts. A considerable amount of experimentation is permissible if the experimentation is merely routine. Ex parte Jackson, 217 U.S.P.Q. 804, 807 (Bd. App. 1982). Each of the tasks described by the Examiner is routinely practiced in the pharmaceutical arts. Accordingly, the rejection of claims 1-28 is improper and Applicant's specification satisfies the requirements of 35 U.S.C. § 112, first paragraph.

Summary:

It is respectfully submitted that the Examiner has not used the correct legal standard for determining enablement under 35 U.S.C. §112, first paragraph. The correct standard was identified in In re Wands. An analysis of claims 1-28 against this standard is provided above. The proper standard is whether practicing the invention would require undue experimentation, not whether the recited compounds will treat all known types of cancer. When all of the factors discussed above are considered as suggested by the court in Wands, the instant application complies with the requirements of 35 U.S.C. § 112.

Claim 1 recites a straightforward method of inhibiting cancer cells, comprising administering to a mammal in need of such therapy, an amount of a compound of formula I effective to inhibit the growth of said cancer cells. Claim 15 recites a straightforward method, comprising contacting cancer cells with an effective amount of a compound of formula I. One skilled in the art can determine whether a given compound of the invention is useful to inhibit a given cancer by running any of a number of assays that are well know in the art. As discussed above, routine screening is permissible and does not represent undue or unreasonable experimentation. Additionally, the claims are directed to an amount of a compound that is effective to produce the recited effect, and therefore inoperative embodiments are excluded. Thus, Applicant respectfully submits that the instant specification adequately enables one skilled in the art to practice the claimed invention without undue experimentation. Accordingly, the instant application complies with the requirements of 35 U.S.C. §112, first paragraph.

The first paragraph of 35 U.S.C. § 112 requires no more than a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of the claims. Applicant's evaluation of the factual considerations outlined by the court in In re Wands demonstrates that the claimed invention can be practiced without undue or unreasonable

experimentation. Accordingly, Applicant respectfully requests withdrawal of the rejection of claims 1-28.

Double Patenting Rejection

Claims 1-7, 10, 12-21 and 26-28 were rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claim 1 of U.S. Patent No. 6,221,892 ("the '892 patent"). This rejection is respectfully traversed.

On page 9 of the Office Action, the Examiner stated that the keto ene-ol tautaumer of a specific ter-benzimidazole of the '892 patent (wherein R_1-R_7 are hydrogen and R_8 is hydroxyl) renders obvious a compound of the instant invention when R_1-R_3 are hydrogen and R_4 and R_5 taken together are -N(H)-C(=O)-N(H)-. Applicant respectfully points out that the compound the Examiner identified (wherein R_4 and R_5 taken together are -N(H)-C(=O)-N(H)-) is not within the scope of applicants claims. Applicant's claims 1 and 15 recite a compound of formula I "provided R_4 and R_5 taken together are not -N(H)-C(H)=N-;" and that the 3, 4, or 5 membered saturated or unsaturated chain (R_4 and R_5 taken together) can be optionally substituted by oxo. The group "-N(H)-C(=O)-N(H)-" identified by the Examiner is the group "-N(H)-C(H)=N-" substituted by oxo. One skilled in the art would understand that the compound identified by the Examiner is excluded from the claims (i.e., is a compound wherein R_4 and R_5 taken together are -N(H)-C(H)=N- substituted by oxo). The claims thus exclude the group -N(H)-C(=O)-N(H)- from their scope of coverage. By properly reading the claim to exclude compounds where R_4 and R_5 taken together are -N(H)-C(=O)-N(H)-, the grounds for the Examiner's rejection is obviated. If the Examiner believes that the claim language is not sufficiently clear, Applicant would be willing to insert the phrase "optionally substituted by oxo" into independent claims 1 and 15 after the phase "provided R_4 and R_5 taken together are not -N(H)-C(H)=N-". Additionally, Applicant points out for the Examiner's convenience that claims 10 and 24, which recited the group identified by the Examiner, have been amended to correct the typographical error, which is discussed and supported at page 8, lines 6-16 of this paper. Accordingly, withdrawal of the rejection of claims 1-7, 10, 12-21 and 26-28 is respectfully requested.

Conclusion

Applicant respectfully submits that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney at (612) 359-3265 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: MS Amendment, Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 29th day of November, 2004.

Patricia A. Hultman

Name

Signature